Case reports

Toxic epidermal necrolysis, agranulocytosis and erythroid hypoplasia associated with sulphasalazine[1]

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Sulphasalazine is used extensively in the treatment of ulcerative colitis. Although minor adverse reactions are well recognized, serious reactions are rare. We report a fatal case of toxic epidermal necrolysis, agranulocytosis and erythroid hypoplasia associated with sulphasalazine therapy.

Case report

A 39-year-old brick moulder was admitted on 13 April 1977 with a six-week history of abdominal pain, diarrhoea and loss of three stones in weight. His bowels were opened six times daily and he passed fresh blood and considerable mucus in his stools.

On examination he was wasted, febrile (temperature 38.3°C) and fluid depleted. There was central abdominal tenderness and guarding. Sigmoidoscopy revealed an ulcerated bleeding rectal mucosa and rectal biopsy confirmed an active proctitis consistent with ulcerative colitis. A barium enema examination showed diffuse ulceration with pseudopolyp formation throughout the whole colon. No pathogens were isolated from his stools and the Widal reaction was negative. He denied taking any drugs before or during his illness and had no history of previous drug allergies or other allergic conditions.

Treatment was commenced with intravenous fluids, intravenous hydrocortisone and oral prednisolone. He also received oral sulphasalazine 1 g twice daily for 4 days and 2 g 4 times daily for 27 days. On admission the patient's haemoglobin was 13.5 g/dl but by 10 May 1977 it had fallen to 11.2 g/dl with a reticulocyte count of 7%. Haematological tests showed no evidence of haemolysis including an absence of Heinz bodies, negative Coombs' and Schumm's tests, and normal plasma bilirubin, haptoglobin and urinary urobilinogen concentrations. Spleen size and function were normal using the 51-chromium labelled heat-damaged red cells test. The fall in haemoglobin was considered to be due to blood loss, fluid repletion and the severity of the illness. His condition improved slowly over 3 weeks, and on 17 May he was discharged home taking sulphasalazine 1 g 4 times daily and oral prednisolone 15 mg daily.

A week later he was well with a haemoglobin concentration of 12.6 g/dl and a white cell count of 7.7×10^9/l. The differential white cell count was normal. However on 8 June he was readmitted because of a severe skin rash. Examination revealed a widespread macular rash involving the trunk, arms and legs with two pustular lesions of the nose and neck. His white blood count was 0.5×10^9/l and bone marrow examination showed an absence of all granulocyte precursors. *Staphylococcus pyogenes* (phage type 77) was isolated from both his nose and pustular skin lesions but blood cultures remained sterile. Sulphasalazine was stopped and treatment was started with intravenous fluids, methylprednisolone and, on the basis of sensitivity tests, with intravenous fucidin and gentamicin. He also received a granulocyte transfusion of 4×10^{10} cells obtained from relatives. On 12 June his haemoglobin and platelet count had fallen to 8.9 g/dl and 45×10^9/l respectively but haematological tests showed no evidence of disseminated intravascular coagulation. His skin rash became confluent giving rise to a generalized erythroderma with blister formation and areas of ulceration. The mouth, eyes and genitals appeared normal. On 13 June his plasma urea had risen to 45 mmol/l and death occurred on the same day with a cardiac arrest.

Autopsy showed a severely hypoplastic marrow involving both red and white cell series. Megakaryocytes were present in normal numbers. The earliest changes in the skin appeared to be spongiosis in the vicinity of the basal layer leading to bulla formation, epithelial necrosis and ulceration (Figure 1). Inflammatory cells were not observed and the appearance was considered consistent with toxic epidermal necrolysis. Fibrin thrombi were observed in the small vessels of the involved areas of the skin and in occasional renal glomeruli. Direct immunoflourescence tests on the skin were negative. Ulcerative colitis was confirmed in the colon.

Discussion

Both sulphasalazine and prednisolone have been reported as being associated with agranulocytosis. Collins (1968) cited 14 cases of agranulocytosis, 5 of which were fatal, and one case of erythroid hypoplasia due to sulphasalazine. There has been only one report of agranulocytosis associated with

[1] Accepted 4 March 1980

0141–0768/80/080587–02/$02.00/0

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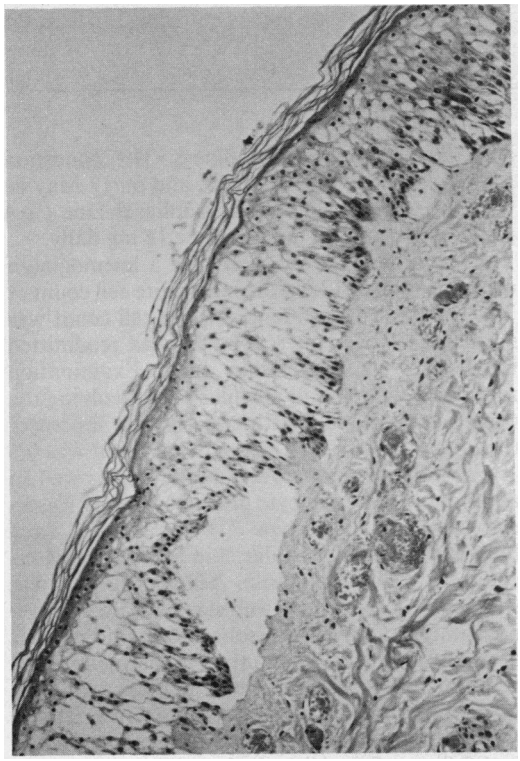

Figure 1. Section of the skin shows subepidermal bullae and spongiosis. Some capillaries in the dermis contain fibrin thrombi. H & E × 190

prednisolone (Rokseth 1960) and it is therefore probable that sulphasalazine was the cause of the agranulocytosis and erythroid hypoplasia in this patient.

Toxic epidermal necrolysis has been described in association with staphylococcal infection (Lyell 1956). The organism is usually phage group II (type 71) and histology reveals superficial epidermal splits. In this patient, however, the epidermal changes and staphylococcal phage type suggested that necrolysis was not due to the staphylococci isolated. Sulphasalazine has previously been implicated as a cause of non-fatal toxic epidermal necrolysis (Strom 1969) and would appear the most likely aetiological factor in this patient.

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0141-0768/80/080588-04/$02.00/0

Hyperornithinaemia with gyrate atrophy of the choroid and retina in two siblings[1]

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The association of hyperornithinaemia (HO) and gyrate atrophy (GA) first described in 1973 (Simell & Takki 1973) has now been reported in at least 30 patients (Takki & Simell 1976, McCulloch & Marliss 1975, Yatziv *et al.* 1979). The condition is due to a deficiency of the enzyme ornithine ketoacid transaminase (OKT) which results in high levels of ornithine in the plasma, cerebrospinal fluid and aqueous humour, low plasma lysine but with normal plasma ammonia levels (Figure 1) (Shih *et al.* 1978). It is transmitted by an autosomal recessive gene.

The two siblings reported here with HOGA are not only the first West Indians to be described but also the first cases to be reported in the British literature. In an attempt to decrease their plasma ornithine levels and thereby slow the progression of the gyrate atrophy they were treated with lysine hydrochloride, a low protein diet and pyridoxine.

Case reports

JM, born in the West Indies in 1965, was referred in 1977 at the age of thirteen to a child psychiatrist because of withdrawn personality and short stature. She suffered severe emotional and physical deprivation until the age of ten years when she came to England. Her parents are unrelated and she has five siblings. She was a withdrawn, small child (height just below, and weight at, the third percentile) with puberty (Stage IV). Apart from myopia her eyes were found to be normal in 1977 but the first changes of GA were noted in 1978 (Figure 2). The initial investigations included urine thin-layer chromatography. The amino acid pattern showed a large band in the ornithine-lysine position, some cystine and one unknown spot. A provisional diagnosis of cystinuria was made but because of the atypical nature of the unknown band urine and plasma were analysed by ion-exchange chromatography. Urinary ornithine was grossly increased and the plasma ornithine level was 10 times normal; the lysine levels were low (Table 1) (Oberholzer & Briddon 1978).

AM, aged seven years, was the only other member of the family found to have the same disorder. She was a normal child, apart from myopia found at the age of six years; changes of GA were first seen in 1978.

[1] Case presented to Section of Paediatrics, 26 October 1979. Accepted 4 March 1980

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